

Research and Development for Health Security: Achievements and Challenges

Progress so far

- 1.** The rise of epidemics has led to devastating consequences for lives and livelihoods around the world. Research and development (R&D), including basic scientific research, social and behavioural, ethics, epidemiology, product development, clinical research, field trials, streamlined regulatory processes, agreements related to product liability, and access and affordability provisions, is critical to understand and prevent infectious disease outbreaks, and to rapidly detect and halt them when they do emerge. However, the window to study these diseases, develop approaches to tackle their spread, and ensure appropriate regulatory and access pathways are in place can be short and infrequent. Moreover, they are often happening in places that lack an established R&D infrastructure. As a result, approaches to R&D have adapted to these different circumstances and will need to continue to do so.
- 2.** In addition to examples of epidemics caused by newly emerged pathogens, persistent, 'slow burn' emergencies such as multidrug-resistant malaria in the Greater Mekong Subregion are increasing, largely in contexts beyond the reach of traditional tools such as long-lasting insecticide-treated nets and indoor residual spraying. Tuberculosis is another example of a disease which has exhibited the 'panic and neglect' cycle of interest and investment that has become a hallmark of these diseases.
- 3.** We have made progress in recent years, with research now widely accepted as a key component of the response to infectious disease outbreaks. The West Africa Ebola epidemic (2014-2016) demonstrated the strides made in the ability to conduct research in outbreaks, and in the increased efforts to accelerate R&D for preparedness. For example, Ebola vaccine rVSV-ZEBOV was trialled in Guinea during the epidemic in 2015, and then implemented in the Democratic Republic of Congo (DRC) epidemic in 2018-2019. Over 100,000 people in DRC have been vaccinated, in an effort that helped manage the spread of the disease in a very challenging situation characterised by security issues, conflict and other humanitarian needs.
- 4.** The WHO has been instrumental in this shift in how research is perceived in the context of epidemic response. A cornerstone was establishing the R&D Blueprint to prioritise, accelerate and coordinate product-related R&D for epidemic risk diseases with no existing treatments. The R&D Blueprint has since created roadmaps for the development of diagnostics, therapeutics and vaccines for diseases such as Lassa fever, Crimean-Congo haemorrhagic fever (CCHF), Ebola/Marburg and Nipah viruses and MERS-CoV. The roadmap processes brought together key actors in each disease to review the evidence and develop priorities to accelerate R&D.
- 5.** There has also been greater investment in R&D related to health emergencies since 2014. The Coalition for Epidemic Preparedness Innovations (CEPI), a product development partnership for vaccines for epidemic risk

diseases established in 2017, has awarded a number of grants for the development of vaccines for diseases on the R&D Blueprint priority list. Other recent initiatives include the European Commission-funded ALLERT and PANDORA-ID-NET networks, which are working to develop research capacity for epidemics in Africa.

6. Capacity building efforts are also paying off, for example in the 2018 outbreak of Nipah virus in Kerala, India, in an area where Nipah hadn't been seen before. A year before the outbreak the US CDC provided in-country training to Manipal Centre for Virus Research (MCRV) and National Institute of Virology (NIV); this training helped to increase diagnostic capacity, and included sharing technical expertise, specific reagents and training for diagnosis of viruses, including Nipah and CCHF. During the outbreak the MCRV and NIV teams were able to rapidly sequence the virus' RNA genome and demonstrate that it was similar to the virus previously detected in West Bengal. This was the first time this was done without transporting samples outside of India. This is also an example of the capacity building occurring through the Global Health Security Agenda (GHSa) and the direct impact on countries' abilities to detect and respond to outbreaks. These examples show the benefits of investing in human resources for health and capacity building to respond to infectious disease outbreaks, particularly in areas that are identified as likely to experience future outbreaks.

7. Another example of progress has been in new approaches to conducting research. For example, the Ebola therapeutics trial led by the Institut National de Recherche Biomédicale (INRB) in DRC and US National Institutes of Health (NIH) is the first Ebola multi-drug, multi-site, multi-country trial, designed to develop evidence during and across outbreaks. Such an approach is necessary given there may not be a sufficient number of patients recruited in any one outbreak to develop an adequate body of evidence on the effectiveness of an intervention.

New Normal

8. Global changes including the rise of fragile states, increased urbanisation, migration, demographic shifts and other social changes, and the risks posed by climate and environmental change, are all shaping the nature and context of infectious disease epidemics. The influences of media (traditional and social) and rapid spread of false information facilitated by technology are impacting public health, as evidenced in cases such as the incitement of violence against Ebola treatment centre staff and discouraging vaccination against preventable diseases such as measles.

9. Our changing world also offers new opportunities to accelerate progress for a world better prepared for health epidemics. More connected societies are able to share information more quickly and cheaply; increased computational power allows us to gather and analyse vast amounts of data more quickly. Developments in technologies such as genetic sequencing, to be faster, more portable and easier to use, mean we can gain new insights into diseases in real time during epidemics, and better predict – and as a consequence, prevent – future epidemics. There is also greater recognition of the importance of early risk identification and planning as part of good governance practice, within both the public and private sectors.

Challenges and Solutions

R&D funding, coordination and governance

10. As R&D is increasingly taking place during outbreak responses, actors in the research and industry community are increasingly required to collaborate with national governments, the WHO and other UN agencies, defence forces, and humanitarian and relief organisations and companies. This poses important questions around the ethics of R&D in these situations, and how actors can most effectively work together (including before epidemics take place) and support capacity of governments, industry, and local implementing partners to guide R&D.

11. More complex settings, especially when outbreaks occur in a humanitarian crises or conflict setting, or across national borders, pose additional challenges for R&D. Actors from humanitarian, defence, public health, industry, and research communities need to work together so that R&D can be carried out. The overlap in the remits of these actors and the plethora of initiatives recently established to support, coordinate or carry out R&D related to health emergencies adds further complexity. Depending on the quality of the relationships in place, this can either result in effective coordination to rapidly identify and implement the most important and urgent activities, or can impede abilities to move swiftly and decisively.

12. While there are global systems in place for health emergencies, a plethora of initiatives and actors in R&D have emerged in recent years, with overlapping interests and remits. However, in certain cases (for example, in vector control), there has been a reduction of potential innovation partners with significant R&D, manufacturing capacity, and routes to market. Now is the time to simplify and create focused global leadership with respect to health emergencies and related R&D to coordinate and speed up innovation. This should facilitate the streamlining of roles and responsibilities for information sharing and ultimately decision making on R&D, so that the global community can move decisively in the event of a health emergency. WHO has a central role in convening and coordinating different actors, and should continue to build the foundations that provide direction and facilitate collaboration, such as the R&D Blueprint and its Global Coordination Mechanism. However, it is important to recognize that other non-state actors (for example, the Bill & Melinda Gates Foundation) are playing an increasing role in public health both in relation to funding as well as policy direction.

13. There are also persistent gaps in R&D for preparedness, despite increased investment such as for diseases on the R&D Blueprint priority list and improved ability to conduct R&D at the country level. For example, there are few international programmes conducting research before and during outbreaks, involving the wide range of actors across research, response, humanitarian communities and national governments in countries at risk. To date, progress in research capacity building for epidemic-related research (ALERRT, PANDORA-ID-NET) has been focused on Africa, overlooking Asia and other regions. The global community must also be mindful of the risk of focusing on solely on pathogens and diseases identified on priority lists; to do so may result in the creation of a new list of neglected diseases, and discounts the reality that non-priority pathogens could potentially become the next epidemic or pandemic. Within this context, it is also important to ensure there is a portfolio of products to address resistant strains, as these may become re-emergent untreatable pathogens.

14. Another priority are investments in R&D related to health emergencies at the country level. Funding core infrastructure and capabilities for prevention,

preparedness and response in countries most at risk is a big gap. To be sustainable, international efforts to build research capacities at country level need to be driven by regional and national priorities, and be relevant to addressing day-to-day issues, such as endemic disease programmes, and not focused on building capabilities that are relevant in the event of a health emergency and/or in contexts of concurrent disease epidemics (such as malaria, HIV/AIDS, and TB).

15. Further, recognising the tensions between the many different actors working to prepare and respond to health emergencies, clear norms and regulations for related R&D (for example, priority review mechanisms) should be developed with engagement of the range interests. These include national governments affected, humanitarian organisations, international agencies, militaries, and research communities, including the private sector. These norms should cover standards of behaviour in the research community to work under rigorous scientific and ethical principles, recognise country interests, and share data and results rapidly and in the public interest. The development process should bring in and build on the work of existing networks and collaborations for R&D, including networks and collaborations with private sector actors.

16. R&D for epidemics has typically been subject to a 'panic and neglect' cycle of interest and investment. Historically, R&D activities of some of the large funders have not been well aligned to each other, or responsive to the needs of response actors and affected countries, creating significant inefficiencies. Communication between donors is important to both ensure there is not excessive duplication of effort, and to ensure the breadth of investment across a diverse range of R&D priorities (i.e., across disease and approaches).

17. There is also a need for increased engagement of new and emerging donors. High income countries cannot close the R&D gap alone. To make a meaningful difference, all countries, especially those with high disease burdens, must invest in bringing new modalities to fruition. Emerging economies like the BRICS and other high-burden countries must also invest their fair share in R&D to finance tomorrow's advances.

18. Regardless of their origin, financial commitments to global health R&D must be long-term in nature. Stringently executed research is both expensive and time-consuming, and requires sustainable funding sources.

Gaps and priorities for R&D

19. While there has been progress made, we need to apply the lessons learned to other areas, and tackle gaps that remain. Rapid diagnostics, therapeutics, and preventive tools and technologies (particularly for vector-borne diseases) are lagging behind vaccines, which have come about through advances such as funding for vaccines development through CEPI and how the partnership has worked to bring together the often-siloed aspects of R&D for vaccines.

20. The accelerated development of rapid diagnostics, therapeutics, and preventive tools, to complement advances in vaccine development already underway, should be a priority for R&D so we can better treat people and test and use vaccines. One underpinning component is developing biological reference materials and clinical care standards for these priority diseases. Biological reference materials improve comparability across research so that efforts build clearly on those that came before them. Clinical care standards

mean that care is consistent and can inform a better-quality evidence base for assessing the effectiveness of new treatments.

21. Equally important to developing new tools is creating appropriate market access conditions, so that newly developed products are able to reach markets and populations in need in an efficient and effective manner.

22. Putting communities at the centre of response has been a fundamental lesson of the recent Ebola and Zika epidemics. R&D for health emergencies needs to be reframed to include the social and behavioural sciences, so that the knowledge and tools developed are more suitable for the real world, and supported by appropriate community engagement and coordination strategies. This research is a cornerstone of preparedness, and WHO and implementing agencies such as UNICEF need to further integrate social and behavioural sciences into their programmes, so that the related evidence shapes community engagement in practice.

23. The needs of special populations, including the very young, the very old, the disabled, and pregnant women, should also be considered in the context of R&D in health emergencies. These groups may be disproportionately affected by an outbreak, but key dosing and safety data may be absent. This could potentially be addressed, at least in part, using translational sciences (e.g., animal models) and experimental medicine platforms, as well as modelling and simulation.

24. The likelihood of emerging diseases is increasing, in some cases in complex environments that are facing conflict and security issues, environmental disasters and weak health systems. Responding to health emergencies in these situations has become a new normal, and requires us to adapt approaches for R&D for preparedness and response so that they remain sustainable into the future. The next epidemic could well be caused by a pathogen not yet known to cause human disease, a so-called 'Disease X', just as SARS emerged and infected over 8,000 people in 29 countries in the early 2000s.

25. To counter the challenges posed by the 'new normal' and the increased likelihood of emerging infectious diseases, investment in different levels and types of preparedness is required. Given environmental, social and biological pressures which are leading to the emergence of new infectious diseases, we need further investment in approaches that can be developed now and mobilised to respond to 'Disease X'. This might include creating platforms for broad spectrum antiviral development for highly infectious respiratory diseases, or platforms that are adaptable for diseases in the same virus family, such as flaviviruses (which include dengue, yellow fever, and Zika viruses). For vector-borne diseases, platforms focusing on vector control and entomological capacity hold great potential to address a range of infectious disease threats simultaneously.

Improving ability to do and use R&D

26. Fast-tracking product development is one thing, but if systems to access treatments and identify effective interventions are not in place, progress made in R&D will not be realised. A key challenge is the lack of clinical research infrastructure in the countries where epidemics are likely to happen. This includes the regulatory frameworks and capacity in place to provide appropriate oversight for research and expertise to assess the risks and make swift decisions. While there have been efforts to fast-track product approval in health emergencies and overcome regulatory challenges, pathways for vaccine and therapeutics licensure are still unclear in many contexts.

27. While building regulatory capacity in countries, and mutual recognition between countries, should be a long-term ambition, there needs to be clear and simplified pathways to licensure to allow fast-track product approval in health emergencies. For example, WHO's Emergency Use Assessment and Listing procedures (EUAL) is currently limited by a very high threshold for product eligibility. Clearer criteria for use of this and other accelerated or emergency assessment and approval pathways are needed.

28. As infectious disease outbreaks will continue to occur in new, different, and more complex places, existing ways of doing R&D and delivering products and interventions may no longer be effective or practical. For example, in 2016 a global shortage of yellow fever vaccine resulting from unexpectedly high demand due to outbreaks in Angola and DRC, led WHO to develop a research agenda for fractional dose yellow fever vaccination, to advance the availability of evidence to inform policy. Another challenge to delivering many life-saving vaccines and therapeutics is that they require refrigeration, yet the infrastructure needed for these cold-chains does not exist in some countries, especially those that have recently faced natural disaster and/or conflict. The global community should encourage and embrace innovative approaches and the use of new technology (or use of existing technologies in new ways).

29. Advances in R&D and product development will only reach their full potential when supplemented by improved surveillance networks, which will enhance our ability to anticipate outbreaks, detect them rapidly when they do occur, and monitor the development of resistance. Improved capacity for the diagnosis and management of febrile illnesses will not only assist in reducing morbidity and mortality from ongoing epidemics such as malaria, but will also establish capacity for surveillance and help to reduce the background of febrile illness, effectively enhancing signal detection for any new or re-emerging pathogen.

30. To ensure that products, interventions and the ways they are delivered are suited to context, we need to adapt the way R&D is done, and broaden our collective scope and understanding of what is included within the mantle of 'global health R&D'. One example is the recent IRNB-NIH Ebola therapeutics trial designed to collect evidence across outbreaks, countries and time, to build a picture of the effectiveness of the four drugs. Further use of adaptive clinical trial models that allow flexibility and real-time learning in crisis settings should be expanded to ensure improved outcomes from R&D conducted in epidemic and field contexts more quickly.

31. Lastly, while there is reason for optimism, it is important to bear in mind that quick "golden bullet" solutions cannot be expected. An effective system for global health R&D demands persistence and stamina, and must be able to withstand failure (which is bound to happen).